REMARKS

Claims 22, 23 and 27-29 are pending in the application.

Regarding 35 U.S.C. § 112, First Paragraph

Written Description

Applicants traverse the rejection of claims 22, 23 and 27 to 29 under 35 U.S.C. § 112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Base claim 22 is directed to a method of identifying a therapeutic agent for treating Alzheimer's disease by performing matings between a first parent strain carrying a mutation in an Alzheimer's disease gene selected from the group consisting of amyloid precursor protein-like (Appl), presenilin (Psn), halothane resistant (har38), cAMP-responsive element-binding protein A (CrebA), cAMP-responsive element-binding protein B (CrebB), α-adaptin, garnet, shibire (shi), Notch (N), Suppressor of Hairless (Su(H)), Delta (Dl), mastermind (mam) and big brain (bib) and a second parent strain containing a genetic variation, whereby test progeny are produced, where, in the absence of an agent, the parent strains produce test progeny having an altered phenotype relative to at least one sibling control; administering an agent to at least one strain selected from the group consisting of the first parent strain, the second parent strain and the test progeny; and assaying the test progeny for the altered phenotype, wherein a modification of the altered phenotype producing a phenotype with more similarity to a wild type phenotype than the altered phenotype has to the wild type phenotype indicates that the agent is a therapeutic agent.

The specification discloses numerous Alzheimer's disease genes with which one skilled in the art can practice the invention and further provides additional exemplary Alzheimer's disease genes, including genes disclosed in the specification itself as interacting (directly or indirectly) with *Appl*. Additional Alzheimer's disease genes that are disclosed in the specification, for example at page 14, as useful for practicing the methods of the invention include, for example, *Notch* (N), *Suppressor of Hairless* (Su(H)), *Delta* (Dl), *mastermind* (mam), *big brain* (bib), *halothane resistant* (har38), *cAMP-responsive element-binding protein A*

(CrebA), *cAMP-responsive element-binding protein B* (CrebB, activator), *cAMP-responsive element-binding protein B* (CrebB, inhibitor), *α-adaptin*, *garnet* (δ-adaptin), and *shibire* (shi)(dynamin). The specification teaches that an Alzheimer's disease gene can be a gene that is differentially expressed at the mRNA or protein level in *Appl*^{d} flies as compared to *Appl*$^{+}$ flies and discloses several dozen specific examples of such Alzheimer's disease genes in Tables 4-6. One skilled in the art would have appreciated that Applicants were in possession of parental strains other than the Drosophila *Appl*^{D}, in sufficient numbers to show possession of the genus of parent strains that carry a mutation in an Alzheimer's disease gene.

Applicants point out that, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the invention (page 17, lines 1-10). In this regard, the specification further describes that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes (*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Applicants respectfully submit that the specification conveys to the skilled person that, at the time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

Applicants submit that the specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

Further with regard to observable phenotypes, the specification teaches that viability is particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of *Appl*^{d} and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly

decreased viability as compared to sibling controls, while flies carrying *Appl*^{d} and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls. With regard to a behavioral phenotype, Example III, shows that Appl^{d} Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant change in the physical appearance or observable properties of the test progeny as compared to a sibling control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 22, 23 and 27 to 29 under 35 U.S.C. §112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Enablement

Applicants traverse the rejection of claims 22, 23 and 27 to 29 under 35 U.S.C. § 112, first paragraph, as lacking enablement of the claimed invention sufficient to teach a skilled person to perform the claimed methods at the time the application was filed.

The specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

The specification teaches that viability is an observable phenotype particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of *Appl*^{d} and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly decreased viability as compared to sibling controls, while flies carrying *Appl*^{d} and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls.

With regard to a behavioral phenotype, Example III, shows that Appl^{d} Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant change in the physical appearance or observable properties of the test progeny as compared to a sibling control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

As taught in the specification, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the invention (page 17, lines 1-10). In this regard, the specification further teaches that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes (*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Applicants respectfully submit that the specification conveys to the skilled person that, at the time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 22 to 29 under 35 U.S.C. §112, first paragraph, as allegedly failing to teach the skilled person how to perform the claimed methods at the time of the invention.

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call Astrid Spain or the undersigned if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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